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WHAT IS THE ROLE OF REVERSAL AGENTS IN THE MANAGEMENT OF EMERGENCY DEPARTMENT PATIENTS WITH DABIGATRAN-ASSOCIATED HEMORRHAGE?

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☐ **Abstract—Background: In 2010, the U.S. Food and Drug Administration (FDA) approved dabigatran as the first non-warfarin oral anticoagulant for use in the United States. At the time of FDA approval, there was no antidote or effective treatment for dabigatran-induced hemorrhage. In 2015, the FDA approved idarucizumab for the treatment of dabigatran-induced hemorrhage. The purpose of this clinical practice statement is to evaluate the role of select reversal agents in the management of patients with dabigatran-associated bleeding. Methods: A PubMed literature review was completed to identify studies that investigated the role of reversal agents in the management of emergency department patients with dabigatran-associated hemorrhage. Articles included were those published in the English language between January 2010 and January 2017, enrolled human subjects, and limited to the following types: randomized controlled trials, prospective trials, meta-analyses, and retrospective cohort studies. Review articles, case series, and case reports were not included in this review. All selected articles then underwent a structured review by the authors. Results: Six hundred fifty-two articles were identified in the search. After use of predetermined inclusion and exclusion criteria, six articles were selected for structured review. Conclusion: The clinical efficacy of activated prothrombin complex concentrates, idarucizumab, and recombinant factor VIIa remains unclear until further research is performed. Activated prothrombin complex concentrates, idarucizumab, and recombinant factor VIIa may be considered in patients with serious bleeding from dabigatran, after careful consideration of possible benefits and risks.** © 2018 Elsevier Inc. All rights reserved.

☐ **Keywords—dabigatran; severe hemorrhage; life-threatening hemorrhage; anticoagulation; prothrombin complex concentrates; recombinant factor VIIa; factor eight inhibitor bypass activity; fresh frozen plasma**

INTRODUCTION

In 2010, the U.S. Food and Drug Administration (FDA)-approved dabigatran as the first non-warfarin oral anticoagulant for use in the United States. Dabigatran is a direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. Indications for dabigatran include the prevention and treatment of deep vein thrombosis and pulmonary embolism, as well as stroke prevention in patients with nonvalvular atrial fibrillation. A primary advantage of dabigatran is that it does not require routine blood monitoring (i.e., international normalized ratio) like warfarin. Importantly, at the time of FDA approval, there was no antidote or established treatment for the reversal of dabigatran in patients with significant hemorrhage.

Shortly after FDA approval, reports of emergency department (ED) patients with significant hemorrhage (i.e., intracranial hemorrhage, gastrointestinal hemorrhage) attributed to dabigatran were published (1). Traditional treatments, including prothrombin complex concentrates (PCCs) and fresh frozen plasma (FFP), were used with variable efficacy. In 2015, idarucizumab was approved by the FDA for the reversal of dabigatran in patients with hemorrhage. Idarucizumab is a monoclonal antibody fragment that binds specifically to dabigatran to neutralize the anticoagulant effect (2). The purpose of this clinical practice statement is to evaluate the role of select reversal agents in the management of patients with dabigatran-associated bleeding.

METHODS

A structured literature review was performed using PubMed to identify articles that investigated select reversal agents in the management of ED patients with dabigatran-associated hemorrhage. The search was limited to studies written in the English language, involved only adult human subjects, and published between January 2010 and January 2017. Studies were also limited to the following types: randomized controlled trials, prospective trials, meta-analyses, and retrospective cohort studies. Review articles, case series, and case reports were not included in this review. Abstracts were identified in two separate literature searches, provided in Table 1. Any abstract that met the initial screening criteria then underwent review by two authors (BH, MW) to determine if the article should be included in this review. References in selected articles were also evaluated to identify any other articles of interest. All included articles underwent a "Grade of Evidence" review by 2 of the study authors (BH, MW) (3). This review was consistent with the established guidelines of the Clinical Practice Committee of the American Academy of Emergency Medicine and is listed in Table 2. All included studies were also provided a separate "Quality Ranking Score" based upon methodology and study design listed in Table 3 (4–9). If a paper was found to be a subset, preliminary, or interim analysis of data that was subsequently published in another paper, only the final or full analysis was reviewed.

Table 1. Literature Search

Tier 1
- A. Keywords used in search: Dabigatran AND Reversal
- B. Database Searched: PubMed
- C. Dates Searched: From 2010 to 2017
- D. Limits Applied
  - Limit: Human
  - Limit: Adult
  - Limit: English
- E. Final Search Results with# of references: 315

Tier 2
- A. Keywords used in search: Dabigatran AND Bleeding
- B. Database Searched: PubMed
- C. Dates Searched: From 2010 to 2017
- D. Limits Applied
  - Limit: Human
  - Limit: Adult
  - Limit: English
  - Limit: Core Clinical Journals
- E. Final Search Results with# of references: 337

Table 2. Definitions of the Criteria Used in Assigning a "Grade of Evidence Review" to the Articles

Grade A	Randomized Clinical Trials or meta-analyses (Multiple Clinical Trials) or Randomized Clinical Trials (Smaller Trials), Directly Addressing the review Issue
Grade B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue
Grade C	Prospective, controlled, nonrandomized, cohort studies
Grade D	Retrospective, nonrandomized, cohort or case-control studies
Grade E	Case series, animal/model scientific investigations, theoretical analyses, or case reports
Grade F	Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

RESULTS

A total of 652 articles were identified by the structured literature review. After use of predetermined inclusion and exclusion criteria, six articles were selected for structured review (Table 4). Three studies were randomized controlled trials, whereas the remaining studies were nonrandomized and cohort studies.

Factor Replacement

Eerenberg and colleagues performed a single-center, randomized, placebo-controlled crossover trial that evaluated the use of four-factor PCC to reverse the anticoagulant effect of dabigatran (4). In this study, 12 male volunteers received 150 mg of dabigatran twice a day for 2.5 days. On the third day, an additional dose was given prior to randomization to an infusion of four-factor PCC (50 IU/kg) or placebo. Dabigatran anticoagulation was assessed using activated partial thromboplastin time (aPTT), thrombin time (TT), and ecarin clotting time (ECT). Four-factor PCC did not reverse the prolongation of aPTT, TT, or ECT in the study subjects. No major or clinically relevant bleeding complications developed in these healthy volunteers.

Marlu and colleagues performed a randomized, crossover trial to evaluate the effect of clotting factor